PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference ITR0069Y	FOR FURTHER ACTION	See Form PCT/IPEA/416
International application No. PCT/US05/02472	International filing date *(day/month/year)* 26 January 2005 (26.01.2005)	Priority date *(day/month/year)* 30 January 2004 (30.01.2004)
International Patent Classification (IPC) or national classification and IPC IPC(7): C07D 211/74; A61K 31/44 and US Cl.: 546/290; 514/346		
Applicant MERCK & CO., INC.		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 4 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *(sent to the applicant and to the International Bureau)* a total of 6 sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) _____ , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).
4. This report contains indications relating to the following items:
   - ☒ Box No. I Basis of the report
   - ☐ Box No. II Priority
   - ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - ☐ Box No. IV Lack of unity of invention
   - ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - ☐ Box No. VI Certain documents cited
   - ☐ Box No. VII Certain defects in the international application
   - ☒ Box No. VIII Certain observations on the international application

Date of submission of the demand	Date of completion of this report
26 August 2005 (26.08.2005)	27 January 2006 (27.01.2006)
Name and mailing address of the IPEA/ US Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (571) 273-3201	Authorized officer Rita J. Desai Telephone No. 571-272-1600

Form PCT/IPEA/409 (cover sheet)(April 2005)

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/US05/02472

Box No. I Basis of the report

1. With regard to the **language**, this report is based on:

☒ the international application in the language in which it was filed.

☐ a translation of the international application into English, which is the language of a translation furnished for the purposes of:

☐ international search (under Rules 12.3 and 23.1(b))

☐ publication of the international application (under Rule 12.4(a))

☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the **elements** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

☐ the international application as originally filed/furnished

☒ the description:
pages 1-61 as originally filed/furnished
pages* NONE received by this Authority on _____
pages* NONE received by this Authority on _____

☒ the claims:
pages 66,68-75 and 77-79 as originally filed/furnished
pages* NONE as amended (together with any statement) under Article 19
pages* 62-65,67 and 76 received by this Authority on 26 August 2005 (26.08.2005)
pages* NONE received by this Authority on _____

☐ the drawings:
pages NONE as originally filed/furnished
pages* NONE received by this Authority on _____
pages* NONE received by this Authority on _____

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, sheets/figs _____
☐ the sequence listing (*specify*): _____
☐ any table(s) related to the sequence listing (*specify*): _____

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages _____
☐ the claims, Nos. _____
☐ the drawings, sheets/figs _____
☐ the sequence listing (*specify*): _____
☐ any table(s) related to the sequence listing (*specify*): _____

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
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Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims 1-18	YES
	Claims NONE	NO
Inventive Step (IS)	Claims 1-18	YES
	Claims NONE	NO
Industrial Applicability (IA)	Claims 1-18	YES
	Claims NONE	NO

2. Citations and Explanations (Rule 70.7)

Claims 1-18 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest the compounds of the invention. The applicants have amended the claims to delete the R1 to be an alkyl or a Hydrogen to overcome the obviousness and novelty objections of Liu et al 2001.

Claims 1-18 meet the criteria set out in PCT Article 33(4), and thus meet the industrial applicability because the subject matter claimed can be made or used in industry.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

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PCT/US05/02472

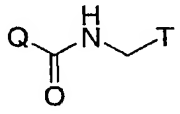
Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

Claim 1-18 objected to as lacking clarity under PCT Rule 66.2(a)(v) because of the claims do not fully supported by the description. The description does not disclose the claimed invention in a manner sufficiently clear and complete for the claimed invention to be carried out by a person skilled in the art because: The scope is so large with the various Hets and there is no examples of the compounds with these het groups. The utility of the compounds is to treat HIV , and the state of the art is still unknown and unpredictable. Pharmaceutical compounds which differ from a hydrogen and a methyl group show a different properties, e.g. theophylline and caffeine differ only by a methyl group and yet differ in properties. One of them is a bronchodilator. Thus when the art is so unpredictable the burden is on the applicant to provide sufficient guidance to show that all the embodiments are enabled.

WHAT IS CLAIMED IS:

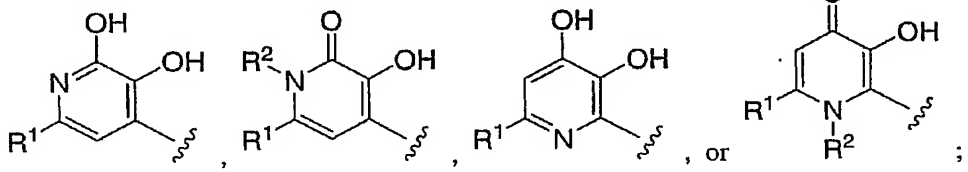
1. A compound of Formula I, or a pharmaceutically acceptable salt thereof:



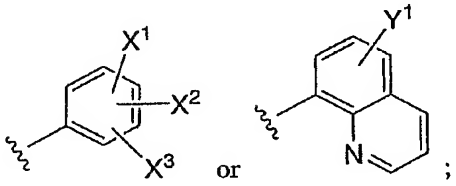
(I)

wherein:

Q is:



T is:



X^1, X^2 and X^3 are each independently selected from the group consisting of -H, halo, -C_{1-4} alkyl, -O-C_{1-4} alkyl, -C_{1-4} fluoroalkyl, -SO_2-C_{1-4} alkyl, -C(=O)-NH(-C_{1-4} alkyl), -C(=O)-N(-C_{1-4} alkyl)$_2$, and HetA

Y^1 is -H, halo, -C_{1-4} alkyl, or -C_{1-4} fluoroalkyl;

R^1 is:

(1) -C_{1-6} fluoroalkyl,

(2) -C_{1-6} alkyl-N(R^a)R^b,

(3) -C_{1-6} alkyl-N(R^a)-C(=O)-R^b,

(4) -C(=O)-R^a,
(5) -C(=O)OR^a,
(6) -C(=O)-N(R^a)R^b,
(7) -C(=O)-N(R^a)-C_{1-6} alkyl-aryl,
(8) -HetB,
(9) -C(=O)-N(R^a)-C_{1-6} alkyl-HetB,
(10) -C_{1-6} alkyl-HetC,
(11) -C(=O)-HetC,
(12) -C(=O)-aryl, or
(13) -C(=O)-HetB;

each HetA is independently a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S, wherein the heteroaromatic ring is optionally substituted with 1 or 2 substituents each of which is independently a -C_{1-4} alkyl ;

HetB is:

(A) a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S; wherein the heteroaromatic ring is attached to the rest of the compound via a carbon atom in the ring, and wherein the heteroaromatic ring is:

(i) optionally substituted with 1 or 2 substituents each of which is independently a -C_{1-4} alkyl; and

(ii) optionally substituted with aryl or -C_{1-4} alkyl-aryl; or

(B) a 9- or 10-membered aromatic heterobicyclic fused ring system containing from 1 to 4 heteroatoms independently selected from N, O and S; wherein the fused ring system consists of a 6-membered ring fused with either a 5-membered ring or another 6-membered ring, either ring of which is attached to the rest of the compound via a carbon atom; wherein the ring of the fused ring system attached to the rest of the compound via the carbon atom contains at least one of the heteroatoms; and wherein the fused ring system is:

(i) optionally substituted with 1 or 2 substituents each of which is independently a -C_{1-4} alkyl; and

(ii) optionally substituted with aryl or -C_{1-4} alkyl-aryl;

HetC is a 4- to 7-membered saturated heterocyclic ring containing at least one carbon atom and a total of from 1 to 4 heteroatoms independently selected from 1 to 4 N atoms, from 0 to 2 O atoms, and from 0 to 2 S atoms, wherein any ring S atom is optionally oxidized to SO or SO_2, and wherein the heterocyclic ring is optionally fused with a benzene ring, and wherein the heterocyclic ring is attached to the rest of the compound via a N atom in the ring, and wherein the heterocyclic ring is:

(i) optionally substituted with 1 or 2 substituents each of which is independently a -C_{1-4} alkyl, -C_{1-4} alkyl-$N(R^a)R^b$, or -$C(=O)OR^a$; and

(ii) optionally substituted with aryl, -C_{1-4} alkyl-aryl, HetD, or -C_{1-4} alkyl-HetD; wherein HetD is (i) a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S or (ii) a 4- to 7-membered saturated heterocyclic ring containing at least one carbon atom and from 1 to 4 heteroatoms independently selected from N, O and S;

R^2 is -C_{1-6} alkyl or -C_{1-6} alkyl-aryl;

aryl is phenyl or naphthyl;

each R^a is independently H or C_{1-6} alkyl; and

each R^b is independently H or C_{1-6} alkyl.

2. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein

R^1 is:

(1) -C_{1-3} fluoroalkyl,
(2) -C_{1-3} alkyl-NH_2,
(3) -C_{1-3} alkyl-NH(-C_{1-3} alkyl),
(4) -C_{1-3} alkyl-N(-C_{1-3} alkyl)$_2$,
(5) -C_{1-3} alkyl-NH-C(=O)-C_{1-3} alkyl,
(6) -C_{1-3} alkyl-N(-C_{1-3} alkyl)-C(=O)-C_{1-3} alkyl,

(7) -C(=O)H,
(8) -C(=O)-C_{1-3} alkyl,
(9) -CO_2H,
(10) -C(=O)O-C_{1-3} alkyl,
(11) -C(=O)-NH(-C_{1-3} alkyl),
(12) -C(=O)-N(-C_{1-3} alkyl)$_2$,
(13) -C(=O)-NH-CH_2-phenyl,
(14) -C(=O)-N(CH_3)-CH_2-phenyl,
(15) -HetB,
(16) -C(=O)-NH-CH_2-HetB,
(17) -C(=O)-N(CH_3)-CH_2-HetB,
(18) -CH_2-HetC,
(19) -CH(CH_3)-HetC, or
(20) -C(=O)-HetC;

HetB is:

(A) a 5- or 6-membered heteroaromatic ring containing a total of from 1 to 3 heteroatoms independently selected from zero to 3 N atoms, zero or 1 O atoms, and zero or 1 S atoms; wherein the heteroaromatic ring is attached to the rest of the compound via a carbon atom in the ring, and wherein the heteroaromatic ring is:

(i) optionally substituted with 1 or 2 substituents each of which is independently a -C_{1-3} alkyl; and

(ii) optionally substituted with phenyl or -CH_2-phenyl; or

(B) a 9- or 10-membered aromatic heterobicyclic fused ring system containing a total of from 1 to 4 heteroatoms independently selected from 1 to 4 N atoms, zero or 1 O atoms, and zero or 1 S atoms; wherein the fused ring system consists of a 6-membered ring fused with either a 5-membered ring or another 6-membered ring, either ring of which is attached to the rest of the compound via a carbon atom; wherein the ring of the fused ring system attached to the rest of the compound via the carbon atom contains at least one of the heteroatoms; and wherein the fused ring system is:

(12) -C(=O)-N(CH_3)-CH_2-phenyl,
(13) -HetB,
(14) -C(=O)-NH-CH_2-HetB,
(15) -C(=O)-N(CH_3)-CH_2-HetB, or
(16) -C(=O)-HetC;

HetB is a heteroaromatic ring selected from the group consisting of oxadiazolyl, thiophenyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, imidazolyl, pyridinyl, pyrimidinyl, pyrazinyl, and pyridoimidazolyl; wherein the heteroaromatic ring is attached to the rest of the compound via a carbon atom in the ring, and wherein the heteroaromatic ring is optionally substituted with methyl or phenyl; and

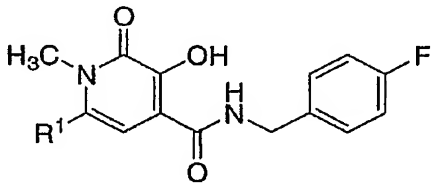
HetC is a heterocyclic ring selected from the group consisting of pyrrolidinyl, morpholinyl, piperidinyl, piperazinyl, and piperidinyl fused with a benzene ring; wherein the heterocyclic ring is attached to the rest of the compound via a N atom in the ring, and wherein the heterocyclic ring is optionally substituted with methyl, -$CH_2N(CH_3)_2$, -C(=O)OCH_2CH_3, pyridinyl, -CH_2-pyridinyl, -CH_2-morpholinyl, or -CH_2CH_2-morpholinyl.

4. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein T is 4-fluorophenyl.

5. The compound according to claim 1, or a pharmaceutically acceptable salt thereof, wherein R^2 is methyl.

6. A compound according to claim 1, or a pharmaceutically acceptable salt thereof, which is a compound selected from the group consisting of:

11. A compound of Formula IV, or a pharmaceutically acceptable salt thereof:



(IV)

wherein R^1 is:

(1) -C_{1-4} fluoroalkyl,

(2) -C(=O)-R^a,

(3) -C(=O)OR^a,

(4) -C(=O)-N(R^a)R^b,

(5) -C(=O)-N(R^a)-C_{1-4} alkyl-aryl,

(6) -HetB,

(7) -C(=O)-N(R^a)-C_{1-4} alkyl-HetB, or

(8) -C(=O)-HetC;

HetB is:

(A) a 5- or 6-membered heteroaromatic ring containing from 1 to 4 heteroatoms independently selected from N, O and S; wherein the heteroaromatic ring is attached to the rest of the compound via a carbon atom in the ring, and wherein the heteroaromatic ring is:

(i) optionally substituted with 1 or 2 substituents each of which is independently a -C_{1-4} alkyl; and

(ii) optionally substituted with aryl or -C_{1-4} alkyl-aryl; or

(B) a 9- or 10-membered aromatic heterobicyclic fused ring system containing from 1 to 4 heteroatoms independently selected from N, O and S; wherein the fused ring system consists of a 6-membered ring fused with either a 5-membered ring or another 6-membered ring, either ring of which is attached to the rest of the compound via a carbon atom; wherein the ring of the fused ring system attached to the rest of the compound via the carbon atom contains at least one of the heteroatoms; and wherein the fused ring system is: